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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,369	02/26/2004	Shozo Koyama	AMN-006-003	3406

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,369	KOYAMA ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-35 and 37-46* is/are pending in the application.

4a) Of the above claim(s) *29-34 and 38-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Claims 29-35 and 37-46 are pending of which, claims 29-34 and 38-46 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03 (see office action of 1/26/07 for withdrawal of non-elected invention).
2. Therefore, claims 35 and 37 are examined on merits.

Rejections Withdrawn

3. Applicant's arguments, see p20, filed on March 11, 2009, with respect to the rejections under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. The rejection of claims 35 and 37 under 35 U.S.C. 112, second paragraph has been withdrawn in view of amended claim 35 in the reply filed on March 11, 2009.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 35 and 37 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is directed to a method for therapy of a cancer in an animal comprising treating cultured cells of said cancer in vitro with a compound of formula 3-a to extinguish the cells, collecting sediment of said treated cultured cells and administering the sediment to said animal.

Specification lacks clear correlation of inhibition of implanted cancer cell growth in animal by sediments of extinguished cancer cell culture produced only by treatment with Yoshixol or Yososhixol 7001. Specification also lacks written descriptive support for the enormous number of compounds encompassed by the compound of formula 3-a useful for therapy of cancer.

As described in the specification, sediments of extinct cultured cancer cells after treatment with "Yoshixol" (i.e. the compound of claim 35 wherein all of R_3, R_4, R_5 and R_6 are hydrogen), when administered into a mice, is shown to slow down the growth of implanted cancer cells and thus improve survival time. As described in the specification, the composition (i.e. sediments of extinct cultured cells recovered after treatment of cancer cell *in vitro* with the compound of formula 3-a) is administered into a mice and then the mice is implanted with cancer cells to show inhibition of growth of the implanted cancer cells. The process as described above is immunotherapy of an animal with cancer cell components extincted with the compound of formula 3-a, for inhibition of cancer cell growth. However, The experiments are not conclusive because the control group in both the cases received cell free medium (see page 41, lines 1-3 of specification and in the affidavit filed 3/11/09), which is not a proper control for cell sediments of treated cancer cell

lines with Yoshixol or Yoshixol 7001. Specification does not have guidance about what components of the extincted cells, when injected into a mouse are responsible for inhibition of growth of implanted cancer cell. Sediments have not been fractionated to identify the compound responsible for this and it is not clear whether the component(s) in the sediment responsible for inhibition of growth of implanted cancer cells are produced only in Yoshixol or Yoshixol 7001 treated cells. Cell sediments (not treated with yoshixol), supernatant (or concentrated supernatant) of cancer cell culture (not treated with yoshixol) and sediments of cancer cell after apoptosis, may have the components responsible for inhibition of the growth of implanted cancer cells and which have not been used as a control in any of the experiments to rule out the involvement of non-treated cancer cell sediments or supernatant to clearly show that only cancer cell sediments that have been treated with Yoshixol or Yoshixol 7001 does have component(s), which when injected in a mice, provides inhibition of implanted cancer cell growth. From the experiments with the control (cell free medium), as disclosed in the specification, one of ordinary skill in the art can not conclude with certainty that only Yoshixol or Yoshixol 7001 treated cells provides inhibition of cancer cell growth in an immunized animal because sediments of cancer cell lysate, supernatant (concentrated) of cancer cell culture and cancer cell sediments after apoptosis, have not used as a control to show clear relationship of Yoshixol or Yoshixol 7001 treated cell and the immunotherapy.

Further, the only compounds shown to inhibit the growth of implanted cancer cells in the specification is Yoshixol (wherein all the substitution group R_3, R_4, R_5

and R_6 are all hydrogen) and the compound Yoshixol 7001 (wherein substitution group R_3, R_4 are hydrogen and R_5 and R_6 forms a fused benzene ring) (as described in 1.132 decoration filed 6/18/08). However, the compound of formula 3-a, as claimed, encompasses a large number of structurally diverse compounds substantially divergent, structurally and functionally from Yoshixol or Yoshixol 7001, when substituted with enormous number of structurally divergent substitution groups. Specification does not provide any clear guidance as to what core component of the compounds is actually having activity responsible for the intended function (i.e. extinction of cancer cells wherein the extincted cell sediments can be used to inject mice to inhibit implanted cancer cell growth). Only example in the specification that provides inhibition of cancer cell growth is with Yoshixol treated sediments of cancer cell, wherein all the substitution group R_3, R_4, R_5 and R_6 are hydrogen and the substitution group hydrogen is not a representative of all the structurally diverse substitution group as claimed because functional groups alkylene, alkoxy, polycyclic hydrocarbon, naphthalene, azulene, haptalene, pentalene, thiophene, pyrrole, Y-pyran, Y-thiopyran, thiozole, imidazole, pyrimidine, indole or quinoline groups are diverse with respect to structure and chemical reactivity and specification does not provide any guidance as to what functional groups would be a representative of substitution group hydrogen having similar reactivity. Similarly, in the compound Yoshixol 7001, substitution group hydrogen (R_3 and $R_{4)}$ and aryl group (R_5 and R_6) are not representative of the entire structurally divergent substitution groups as claimed because they posses different chemical

reactivity and specification does not establish a representative functional groups or a representative core structure that would represent a closely related structural compound(s) with similar properties representative of Yoshixol.

Therefore, an artisan in the art would not be able to practice full scope of the invention because an undue experimentation will be required to judge suitability of the representative compounds encompassed by formula 3-a useful for treatment of cancer. Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Response to argument

6. Applicant's arguments, amendments and affidavit filed 3/11/09 have been fully considered and are persuasive to overcome the rejections under 35 USC 112, second paragraph. However, the Applicants' amendments, arguments and affidavit are not persuasive to overcome all the issues of the rejection under 35 USC 112, first paragraph mailed 10/8/08.

Applicants argued that by the amendment to claim 35, the compound of Formula 3-a is restricted to Yoshixol or a polycyclic compound yoshixol-2001, which the Applicant has already demonstrated to have a therapeuric effect on cancer, and to compounds having a structure reasonable similar thereto and in view of the

strucrtural similarity of the compounds, applicants submit that a person of ordinary skill in the art would expect the compounds to exhibit similar effects and that, therefore, amended claim 35 is properly supported by the data for Yoshixol and Yoshixol-7001.

Applicants' arguments have been fully considered but are not persuasive because the Examiner maintains that the compound of formula 3-a, as claimed, encompasses a large number of structurally diverse compounds substantially divergent, structurally and functionally from Yoshixol or Yoshixol 7001, when substituted with enormous number of structurally divergent substitution groups. Specification does not provide any clear guidance as to what core component of the compounds is actually having activity responsible for the intended function. Only example in the specification that provides inhibition of cancer cell growth is with Yoshixol treated sediments of cancer cell, wherein all the substitution group R_3, R_4, R_5 and R_6 are hydrogen and the substitution group hydrogen is not a representative of all the structurally diverse substitution group as claimed because functional groups alkylene, alkoxy, polycyclic hydrocarbon, naphthalene, azulene, haptalene, pentalene, thiophene, pyrrole, Y-pyran, Y-thiopyran, thiozole, imidazole, pyrimidine, indole or quinoline groups are diverse with respect to structure and chemical reactivity and specification does not provide any guidance as to what functional groups would be a representative of substitution group hydrogen having similar reactivity. Similarly, for the compound Yoshixol 7001, fused benzene substitution group (R_5 and R_6) are not representative of the structurally divergent substitution

groups such as polycyclic hydrocarbon, naphthalene, azulene, haptalene, pentalene, thiophene, pyrrole, Y-pyran, Y-thiopyran, thiozole, imidazole, pyrimidine, indole or quinoline as claimed because they posses different structure and are divergent with respect to chemical reactivity and specification does not establish a representative functional groups or a representative core structure that would represent a closely related structural compound(s) with similar properties representative of Yoshixol or Yoshixol-7001.

Further, with regard to rejection for proper control group for culture cell sediments (see rejection of 10/8/08 and paragraph 5 of this office action), the data in the specification is deficient in correlating inhibition of implanted cancer cell growth in an animal by sediments of extinguished cancer cell culture produced only by treatment with Yoshixol or Yososhixol 7001. That is the data in the specification and the experiments in the affidavit filed 3/11/09 failed to clearly establish that cell sediments produced only by Yoshixol or Yoshixol-7001 treated cells provides inhibition of cancer cell growth implanted in an animal because proper cell sediment control(s) have not been used and Applicants failed to address this issues. As described in the specification, sediments of extinct cultured cancer cells after treatment with "Yoshixol" (i.e. the compound of claim 35 wherein all of R_3, R_4, R_5 and R_6 are hydrogen), when administered into a mice, is shown to slow down the growth of implanted cancer cells and thus improve survival time. As described in the specification, the composition (i.e. sediments of extinct cultured cells recovered after treatment of cancer cell *in vitro* with the compound of formula 3-a) is administered

into a mice and then the mice is implanted with cancer cells to show inhibition of growth of the implanted cancer cells. The process as described above is immunotherapy of an animal with cancer cell components extincted with the compound of formula 3-a, for inhibition of cancer cell growth. However, The experiments are not conclusive because the control group in both the cases received cell free medium (see page 41, lines 1-3 of specification and in the affidavit filed 3/11/09), which is not a proper control for cell sediments of treated cancer cell lines with Yoshixol or Yoshixol 7001. Specification does not have guidance about what components of the extincted cells, when injected into a mouse are responsible for inhibition of growth of implanted cancer cell. Sediments have not been fractionated to identify the compound responsible for this and it is not clear whether the component(s) in the sediment responsible for inhibition of growth of implanted cancer cells are produced only in Yoshixol or Yoshixol 7001 treated cells. Cell sediments (not treated with yoshixol), supernatant (or concentrated supernatant) of cancer cell culture (not treated with yoshixol) and sediments of cancer cell after apoptosis, may have the components responsible for inhibition of the growth of implanted cancer cells and which have not been used as a control in any of the experiments to rule out the involvement of non-treated cancer cell sediments or supernatant to clearly show that only cancer cell sediments that have been treated with Yoshixol or Yoshixol 7001 does have component(s), which when injected in a mice, provides inhibition of implanted cancer cell growth. From the experiments with the control (cell free medium), as disclosed in the specification, one of ordinary skill

in the art can not conclude with certainty that only Yoshixol or Yoshixol 7001 treated cells provides inhibition of cancer cell growth in an immunized animal because sediments of cancer cell lysate, supernatant (concentrated) of cancer cell culture and cancer cell sediments after apoptosis, have not used as a control to show clear relationship of Yoshixol or Yoshixol 7001 treated cell and the immunotherapy.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bystryn (US 5030621, US 5635188, US 6338853 and US 5194384) discloses supernatant of cancer cell culture to immunize a patient in the treatment of cancer.

McCollester (US 4,720,386) discloses disrupted cancer cell material as immunogenic component for immunization for regression of cancer through stimulation of patient's immune response.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicant should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in ipsis verbis, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641